**2018 IMAG Futures Meeting – Moving Forward with the MSM Consortium (March 21-22, 2018)**

**PI(s) of MSM U01: Colleen E. Clancy**
**Institution(s): University of California, Davis**
**MSM U01 Grant Number:** 5U01HL126273-03
**Title of Grant:** PREDICTIVE MULTISCALE IN SILICO CARDIO-PHARMACOLOGY

**Abstract Authors**

Pei-Chi Yang[1], Laura L. Perissinotti[3], Yibo Wang[3], Kevin R. DeMarco[1], Mao-Tsuen Jeng[1], Igor Vorobyov[1,2], Vladimir Yarov-Yarovoy[1], Sergei Y. Noskov[3], and Colleen E. Clancy[1,2]
[1] Department of Physiology and Membrane Biology, School of Medicine, University of California, Davis; [2] Department of Pharmacology, School of Medicine, University of California, Davis; [3] Centre for Molecular Simulation, Department of Biological Sciences, University of Calgary

**Abstract Text**

**Elucidating sex dependence of cardiac arrhythmias via multiscale modeling and simulations**

Heart rhythm disturbances, such as long QT syndrome (LQTS), have been linked to mutations in cardiac ions channels, as well as unintended drug interactions with these channels. Female sex has been shown to be an independent risk factor for both inherited and acquired LQTS and associated Torsade de Pointes (TdP) arrhythmias, and sympathetic discharge is a major factor in triggering TdP in female LQTS patients. Both experimental and modeling studies have demonstrated that this phenomenon is likely related to differential levels of sex hormones (estradiol, progesterone and testosterone) playing opposite roles in pro-arrhythmia proclivities, exacerbating or mitigating effects of ion channel mutations or drug-induced blockade. We developed multiscale mathematical models of acquired and inherited LQTS in human male and female ventricular myocytes and cardiac tissues by combining effects of a hormone, sympathetic stimulation and a hERG channel blocker, dofetilide, or hERG mutations. These models predicted that an increased risk for both inherited and acquired LQTS associated arrhythmias in females upon acute sympathetic nervous system discharge is correlated with higher levels of estrogen, whereas progesterone or testosterone (for males) mitigated arrhythmogenesis. Our atomistic structural modeling and simulations demonstrated possible interactions of estrogen with TdP-inducing hERG pore blockers such as dofetilide and sotalol in an intra-cavity binding site, and also with a site in the hERG pore loop containing a known arrhythmogenic G604S mutation. This study represents a successful application of a multiscale modeling methodology linking atomic structure to functional mechanisms underlying female dominance of LQTS associated arrhythmias.